Claims

1. Recombinant adenovirus with changed tropism, characterized in that the native pentone fibre, comprising a fibre tail, a fibre shaft and a fibre knob including a trimerisation motif, has been changed in that the native knob containing the cell binding structure and the native trimerisation motif has been removed and a new cellbinding ligand and an external trimerisation motif have been introduced into the virus fiber.

2. Adenovirus according to claim 1, chracterized in that said structural modification has been performed by DNA technology at the gene level or by chemical or immunological means at the virus level.

3. Adenovirus according to claim 1 which is either replication competent or replication in-competent.

4. Adenovirus according to claim 1, characterized in that the new cellbinding ligand has been introduced into the fiber shaft.

5. Adenovirus according to claim 1, characterized in that the new cell binding ligand has been introduced downstream of the fiber shaft repeats.

6. Adenovirus according to claim 4 characterized in that the new cellbinding ligand has been introduced between the restriction sites Nhe1 and Hpa1 in the fiber shaft.

7. Adenovirus according to claim 4, characterized in that amino acid linkers have been introduced upstream and downstream of the cellbinding ligand.

8. Adenovirus according to claim 4, characterized in that the shaft repeats downstream of the restriction site Hpa1 have been removed.

9. Adenovirus according to claim 1, characterized in that an amino acid linker motif has been added between the fiber shaft and the trimerisation motif and/or between the trimerisation motif and the cellbinding ligand as a linker.

10. Adenovirus according to claim 9, characterized in that the amino acid linker motif is any of the following: SEQ ID NO: 3, derived from Psedomonas exotoxin; SEQ ID NO: 4, derived from tissue prothrombin activator; SEQ ID NO: 5, derived from the hinge region of mouse immunoglobulin; SEQ ID NO: 6, derived from Staphylococcal protein A; SEQ ID NO: 7, derived from the hinge region of human IgG3 ; SEQ ID NO: 8, derived from shaft repeat 17 of human Ad5.

11. Adenovirus according to any of the claims 1 - 10, characterized in that the new cellbinding ligand is any cellbinding peptide.

12. Adenovirus according to claim 11, characterized in that the cell binding ligand is a monoclonal antibody or a fragment thereof whether as a single chain fragment or Fab, a T cell receptor or a fragment thereof, an integrin binding peptide such as RGD or a growth factor such as Epidermal Growth Factor.

13. Adenovirus according to claim 12, containing any of the sequences SEQ ID NO: 10 - 12.

14. Adenovirus according to claim 12, characterized in that the single chain fragment is a single chain fragment of the monoclonal antibody G250 with heavy chain variable

region with SEQ ID NO: 15 and light chain variable region with SEQ ID NO: 16.

15. Adenovirus according to claim 1 characterized in that the external trimerisation motif is an α-helical coiled coil motif ,or any other peptide capable of rendering functionally trimerised fibers.

16. Adenovirus according to claim 15, characterized in that the external trimerisation motif is the neck region peptide of human lung surfactant protein D, SEQ ID NO: 1 or a 31 aa "Zipper" motif where the leucine residues on positions 1 and 4 have been replaced with isoleucine residues, SEQ ID NO: 2.

17. Adenovirus according to any of the preceding claims characterized in that an external nuclear localisation signal (NLS) has been introduced in the fiber.

18. Adenovirus according to claim 17, characterized in that the NLS is the SV40 large-T antigen NLS.

19. Adenovirus according to any of the preceding claims characterized in that the fiber in addition contains sequences which increase the survival of the fiber in the cytosol of infected cells, thereby enhancing transportation into the nucleus and virus assembly.

20. Adenovirus according to claim 19, characterized in that the sequences are present in the wild type knob.

21. Adenovirus according to claim 20, characterized in that the sequences are present in SEQ ID NO: 10 - 12.

22. Adenovirus according to claims 1 - 21 for the treatment of human diseases, either in vivo or by in vitro methods.

23. A method of producing a recombinant adenovirus with changed tropism, comprising:

I. rescuing recombinant adenovirus fibres into the adenovirus genome by the following steps:

a) subcloning of a 9kb fragment (from Spe1 to end of genome),

b) further subcloning of a 3kb fragment between Sac1 and Kpn1,

c) deletion of the native fibergene coding for the native penton fibre between Nde1 and Mun1 and replacing the missing sequence with the sequence SEQ ID NO: 13 containing an Xho1 site;

d) ligation of recombinant fiber gene coding for between Nde1 and Xho1 of construct under c) above;

e) re-introduction of construct under d) above into the 9 kb fragment cut with Nhe1 using homologous recombination in E. coli;

f) isolation of the recombinant 9 kb fragment under e) and re-creation of the adenovirus genome by joining 9 kb fragment to the 27 kb fragment from the beginning of the genome to the Spe1 site by Cosmid cloning; and

II. transfecting a cell with the adenovirus obtained in step f) to enable said cell to express the recombinant adenovirus.